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Synthesis of 3-Substituted-4*H*-1,4-Benzoxazines *via* Palladium-Catalysed Coupling Reactions

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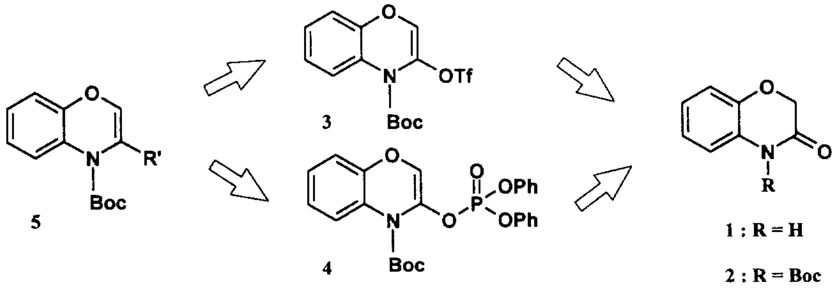
Abstract : Here is described a high yield synthesis of 3-substituted 4*H*-1,4-benzoxazines *via* palladium-catalysed coupling reactions between organostannanes and a vinylphosphate obtained from a benzoxazin-3-one derivative.

Keywords: benzoxazines; coupling reactions; palladium and compounds; tin and compounds

In the course of a research program directed toward the design of biologically active derivatives containing a 1,4-benzoxazine subunit, we needed to have easy access to substituted 4*H*-1,4-benzoxazines. We recently reported a quite general procedure allowing the synthesis of 3-substitued-4*H*-1,4-benzoxazine *via* the regioselective lithiation-electrophilic substitution of the 4-Boc-4*H*-1,4-benzoxazine.[1] However the key step in the preparation of this insaturated carbamic derivative from the corresponding 2,3-dihydrobenzoxazine involves a bromation-debromation sequence that is not easily achievable on a large scale.

We decided to search for a new alternative and complementary method allowing an efficient and rapid synthesis of 1,4-benzoxazines, particularly derivatives bearing aryl, heteroaryl and vinyl groups at C_3. A few years ago Kocienski described the synthesis in good yields of 6-(trimethylstannyl)3,4-dihydro-2*H*-pyrans from δ-valerolactones *via* the Pd(0) catalysed coupling of enol triflate derivatives with hexadimethylstannane.[2] Recently Hiemstra described the synthesis of lactam-derived enol triflates and their functionalization *via* catalytic coupling reaction with Pd(0).[3]

We postulated that 3-substituted-4*H*-1,4-benzoxazines could be obtained in a similar way from the benzoxazin-3-one **2** *via* the enol triflate **3** (Scheme 1).



Scheme 1

The lactam **1** was first prepared from 2-aminophenol[4] in 80 % yield; the N-Boc derivative **2** was then obtained in 96 % yield by treatment of **1** with di-*tert*-butyldicarbonate in dry tetrahydrofuran at room temperature in the presence of DMAP. The N-Boc benzoxazinone was treated with LDA (1.2 eq.) and TMEDA (1.2eq.) at -78°C in dry tetrahydrofuran. The corresponding lithium enolate was reacted then with

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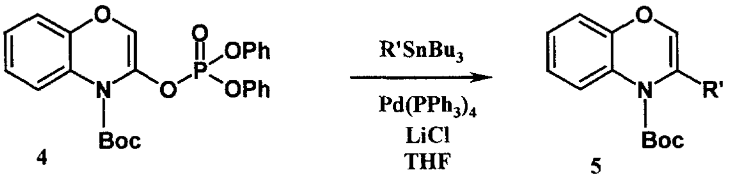
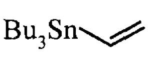
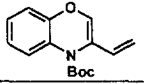
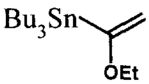
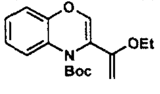
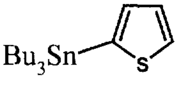
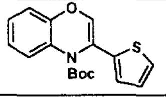
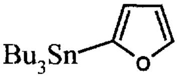
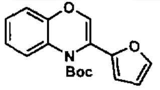
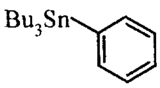
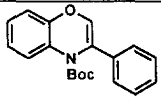
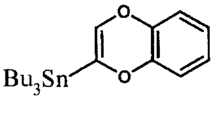
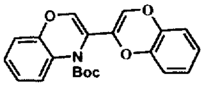
N-phenyltrifluoromethanesulfonimide which probably afforded the required enol triflate; unfortunately this compound decomposed when the temperature exceed -50°C and could not be used further. The lack of stability of cyclic ketene acetal triflates was previously mentioned by Nicolaou who prepared and advantageously used cyclic ketene phosphates.[5] Likewise, we chose to prepare the diphenylphosphate **4** from **2** *via* its lithium enolate (LDA, 1.2 eq.; TMEDA, 1.2 eq.; $(PhO)_2P(O)Cl$, 3eq.; THF; -78°C); the phosphate obtained in 86 % yield proved to be stable enough at room temperature and could be purified by flash chromatography on silicagel.

Coupling the intermediate **4** with various vinyl, aryl and heteroaryl stannanes (2 eq.), in the presence of LiCl (3 eq.) and a catalytic amount of $Pd(PPh_3)_4$ (0.05 eq) in THF at reflux resulted in the formation of 3-substituted derivatives **5** (Table 1).



4 **5**

Table 1. Palladium-Catalysed Coupling of vinyl phosphate **4** with organostannanes $R'SnBu_3$

5	$R'SnBu_3$	Product	Yield
5a			87 %
5b			82 %
5c			91 %
5d			96 %
5e			84 %
5f			93 %

In summary we have developed a new versatile method for the preparation of the little known 3-substituted-4*H*-1,4-benzoxazines.

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